



# Chronic Lymphocytic Leukemia For GPs

By Kuljit Grewal

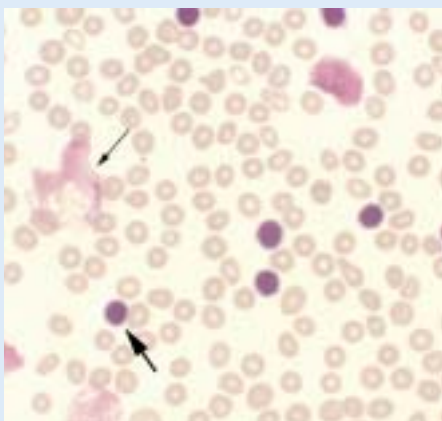
## Case

Jim, 75, presented to his family doctor with shortness of breath that had increased over a couple of weeks. His physical exam showed diffuse adenopathy with nodes measuring 2 cm in the neck, axilla and groin. His spleen was palpable 4 cm below the left costal margin.

His initial complete blood count was:

- WBC 70,000 10<sup>9</sup>/L,
- HB 60 g/L
- MCV 95 FL
- Platelets 41 10<sup>9</sup>/L

The differential showed 88% lymphocytes and 9% neutrophils (see smear below).



Smear of chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the Western world with an incidence of 2.7 per 100,000. It was first described in 1845 and accounts for 0.8% of all cancers. However, there are major differences in incidence rates between countries with Canada having a 26-fold higher rate than Japan.<sup>1</sup>

The disease is rare in persons less than 30 years of age and its incidence increases sharply after the age of 40. Only 15% of patients diagnosed with CLL are younger than 50.<sup>2</sup> Most patients are between 60 and 70 years of age when diagnosed with CLL.

The etiology of CLL remains unknown, with no proven links to occupational exposures. There has been no increased risk shown with radiation exposure or other environmental exposures. Most cases occur sporadically, with rare multiple cases in a single family.

## Biology

CLL is a disease where there is impaired cell death (apoptosis) leading to the accumulation of mature lymphocytes. The cells are usually  $\beta$  cell in origin and are not dividing rapidly.<sup>3</sup>

# Leukemia

Table 1

## Staging

In North America the commonest staging system is the Rai classification.<sup>5</sup>

Stage	Description	Risk	Medial Survival
0	Lymphocytosis in blood/marrow	Low	> 10 years
1	Lymphocytosis + adenopathy	Low	> 10 years
2	Lymphocytosis + splenomegaly	Intermediate	7 years
3	Lymphocytosis + anemia	Intermediate	7 years
4	Lymphocytosis + thrombocytopenia	High	1.5 years

## Clinical Presentation

Many patients are entirely asymptomatic and are diagnosed, incidently, during routine blood work (CBC) or because of palpable lymph nodes noted by the patient or relative. Those that do have symptoms present with symptoms due to anemia, thrombocytopenia, recurrent infections, fever, weight loss, night sweats, fatigue, and splenic discomfort.

During the clinical exam, one should look for the presence of adenopathy, splenomegaly and hepatomegaly. If nodes are present, they tend to not be massive, diffusely distributed, firm and non-tender to palpation. The physical exam is entirely normal in up to 30 % of individuals.



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## Diagnosis

The diagnosis can usually be made on a routine complete blood count (CBC) and peripheral smear. There is an elevated white count with an absolute lymphocyte count greater than  $5 \times 10^9/L$ . The hemoglobin may be normal or decreased as may the platelets.

The smear will show small mature lymphocytes with “smudge cells.” The diagnosis is confirmed by performing immunologic tests on the blood. Flow cytometry shows a population of lymphocytes which co-express  $\beta$  cell markers CD 19, 20, 23 and T cell marker CD5.<sup>4</sup> Bone marrow is rarely needed for diagnosis, although it may help in determining prognosis. If there is extensive peripheral adenopathy, a computed tomography (CT) scan may be useful.

## Complications

These patients are at risk of developing a number of different complications. The most common is the development of autoimmune hemolytic anemia (AIHA), which occurs in 10% to 20% of cases. Up to 5% of patients with AIHA will develop immune thrombocytopenia (ITP).<sup>6</sup> Rare complications include a marked decrease in red cell precursors in the bone marrow, leading to pure red cell aplasia. Also, the CLL can convert to a more aggressive disease, such as a high grade lymphoma (Richter's transformation) or prolymphocytic leukemia. These individuals are also at a higher risk of developing secondary malignancies, such as brain and lung tumors.<sup>7</sup> There is no evidence that the rate of acute leukemia is increased in these patients.

## Treatment

There is currently no curative therapy available for this disease. Many patients are asymptomatic, most are elderly and have an indolent disease process. Therefore, they should be treated only if their symptoms include extreme fatigue, weight loss, extensive sweats, significant anemia, thrombocytopenia, neutropenia, bulky painful adenopathy, painful splenomegaly, and recurrent infections.

If none of these symptoms are present, the patient should be followed with a “watch and wait” approach. At the onset patients can be watched for two to three years before treatment is necessary.<sup>8</sup>

When treatment is needed, there are a number of therapies available, including single-agent chemotherapy such as chlorambucil; nucleoside



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\* Comparative clinical significance has not been established.

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REFERENCES: 1. Oxeze® Turbuhaler® (Formoterol fumarate Dihydrate) Product Monograph, AstraZeneca Canada Inc.

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# Leukemia

## Discussion

This gentleman presents with advanced Stage IV chronic lymphocytic leukemia. He had not had any blood work in the previous four years, but likely has had this disease process for years. Flow cytometry on the peripheral blood confirmed  $\beta$  cell CLL. He was transfused packed cells and started on oral chlorambucil 24 mg per day for five days to be repeated on a monthly basis.

analogs such as fludarabine; combination chemotherapy (*i.e.*, cyclophosphamide, vincustine and prednisone; cyclophosphamide, hydroxycarbonyl and prednisone vincustine), biologic therapies (*i.e.*, CAMPATH-1H), rituximab, and bone marrow transplantation.

Initially, the less toxic therapies, such as oral chlorambucil or intravenous fludarabine, are used. The other treatments are used when the disease is resistant to initial therapy or is rapidly progressing. It is important to note that for those patients with advanced disease the outlook has not improved over the last few decades.

The GP should follow these patients every three to six months watching for symptoms of fatigue, night sweats, weight loss or infections. The exam should focus on the presence of adenopathy and hepatosplenomegaly. The only blood test needed is a CBC and differential. If the white blood count is climbing rapidly (*i.e.*, lymphocyte count is doubling in less than 12 months), this indicates the disease is active and may require treatment soon.

Infection is a major cause of death in patients with increasing white blood cells.<sup>9</sup> The increased risk has multiple factors related to both the disease and the treatments. The most common organisms identified are *staphylococcus*, *streptococcus*, pneumonia and hemophilus influenza. There is often hypogammaglobulinemia, and some patients benefit from replacement of immunoglobulin G. Even

though the response to immunization is suboptimal in some patients due to impaired immunity, these patients should have their vaccinations up to date and receive a flu shot.

## Conclusion

CLL is a common hematologic malignancy with numerous complications. It remains incurable, but patients can live many years with the disease. It is to be hoped that clinical studies into the biology of the disease will lead to promising new therapies. [CME](#)

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